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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/314,540	05/19/99	LANGER	R 0492611-0/5

EXAMINER	
STROUP, C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev 2/95)

U.S. G.P.O. 1999 460-693

Office Action Summary

Application No.	Applicant(s)
09/314,540	Langer et al
Examiner	**Group Art Unit**
Stroup, Carrie	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-63 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-63 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 55 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' claimed invention is to a method of site specific delivery of a therapeutic agent, or combinations thereof. It is noted that the specification provides no teachings on the use of any specific therapeutic agent, but instead relies upon general classifications, such as anti-AIDs substances. It also does not disclose which class of agents should be co-delivered for the treatment of any disorder. Thus, the scope of the claims include numerous combination, resulting in a genus of agents which are highly variant because of the diverse diseases treated with groupings of peptides, DNA, and RNA. Composition variance between genus members is permitted, yet the specification does not provide guidance as to specific changes to make. Functional features that could distinguish compounds in the genus from others are missing from the disclosure. No common structural or functional attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, therapeutic agent alone is insufficient to describe the genus. One of skill in the art would reasonable conclude that

the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

3. Claims 12, 16, 22, 23, 31, 41, 42 and 55-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants' claimed invention is to a composition, its use in a method of making a biomaterial architecture, and methods of use of a biomaterial architecture comprising a biodegradable polymer, such as PLA-PEG, to which an anchor-adapter-tag unit is attached, such as a hapten/antibody complex (claims 12, 16, 22, 23, 31, 41, and 42). It is noted that the specification fails to disclose any specific hapten/antibody complex, or methods of fabricating such within a polymer, such as the disclosed nanosphere. Although antibody binding to the surface of nanospheres and other polymers are routine in the art for targeted delivery (see Domb et al, US Patent 6,007,845, col 15, lines 15-30), it is not generally known in the art the use of a hapten for use in conjunction with the antibody, or how such would even be fabricated. Therefore, it would require undue experimentation by one of skill in the art to make and use a composition comprising a hapten/antibody anchor-tag complex in a biodegradable polymer.

Applicants' claimed invention is also to a method for site specific delivery of therapeutic agents comprising providing a composition of a biomaterial architecture, such as PLA-PEG-biotin and a therapeutic agent associated therewith (claims 55-63). It is unclear from the reading of the specification and the claims if the therapeutic agent is fabricated within the polymer, such as PLA-PEG, or if it is attached as the ligand to the avidin. The specification relies on generalities such as disclosing a method for site specific delivery which involves "a therapeutic agent associated with the biomaterial architecture" (pg 11, line 19), wherein the preferred architecture is a nanoparticle (pg 12, lines 12-14).

The specification fails to provide an enabling disclosure for the method of site specific delivery because it fails to provide a sufficient disclosure on the method of making the claimed biomaterial architecture with the therapeutic agent. The specification has not provided teachings specific to the method of making a PLA-PEG nanoparticle, or any copolymer, with a therapeutic agent, such as the claimed anti-AIDs substances, anti-cancer substances, and analgesics. For example, teachings pertaining to fabrication, mixing, precipitation conditions, quantities and timing of addition of the therapeutic agent to the co-polymer. The specification also fails to disclose the effect of the attached anchor-tag system to the ability of the copolymer to provide the therapeutic agent in a controlled release manner. For example, do the biotin-avidin-ligand attachments sterically hinder the release of any agent from the polymer? (See Domb et al, US Patent 6,007,845, col 19-20, Example 21).

The specification also fails to provide an enabling disclosure for the use of any anti-sense agent, or combinations of therapeutic agents. The specification provides no disclosure of an anti-sense sequence. Applicant is reminded that the art of anti-sense therapy is highly unpredictable, largely due to the lack of stability and specificity exhibited by most oligonucleotides *in vivo* (Branch, A.D, full article). Specifically the specification does not teach the stability of any antisense sequence in vivo, effective delivery to target tissues within an organism, appropriate therapeutic dosages, nor the ability of any sequence to enter a cell and result in a therapeutic effect. Therefore, it would require undue experimentation by one of skill in the art to deliver any antisense molecule via the claimed method and have it result in a therapeutic outcome. The specification also fails to disclose any combination of the claimed therapeutic agents, their relative dose ratios, how to fabricate both within a copolymer, such as a nanosphere, what their relative rates of delivery or diffusion are from the polymer, and so forth. Therefore, it to would require undue experimentation by one of skill in the art to utilize the claimed invention to deliver any therapeutic agent, or a combination of agents.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 55-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 55-63 are unclear as to the use of "ligand" and "therapeutic agent" with the composition. Are they synonymous components within the composition, or is the therapeutic agent attached to the end of the ligand?

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1-11, 13-15, 17-21, 24-30, 32-40, and 43-54 are rejected under 35 U.S.C. 102(a) as being anticipated by Patel et al (11/1998).

Applicants' claimed invention is to a composition, method of making such, and methods of use comprising PLA-PEG biodegradable polymer and a two or three component anchor-adapter-tag system, such as a biotin/avidin or streptavidin system, to which a ligand is attached, such as a peptide, protein, DNA; and a method for the modification of a biomaterial architecture with and without an adapter segment; and a method for tissue engineering comprising providing a scaffold having a biological ligand attached and contacting cells and seeding cells in a bioreactor.

Patel et al disclose a composition, its use in method of making a biomaterial architecture, and methods of using said architecture in tissue engineering for the deliver of therapeutic agents, for use in tissue regeneration of aortic endothelial cells and PC12 nerve cells. Said composition comprised the synthesis of a PLA-PEG-biotin (anchor-adapter) biomaterial architecture to which avidin (tag) binded, and to which alternative a biotinylated therapeutic ligand or an RGD ligand could attach to the avidin , such as the exemplified biotin-RGD attachment for binding to endothelial cells (Figure 1 & col 1, para 2, pg 1449). The method disclosed further comprised seeding the cells attached to the PLA-PEG-biotin architecture in a bioreactor, such as a humidified incubator, for facilitation of cell differentiation into tissue (cp 1449, col 2, para 1). Patel et al also teach that the architecture could comprise a wide range of ligands (pg 1453, col 1, para 2). Therefore, the claimed invention was clearly anticipated.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

9. Claims 1-11, 13-15, 17-21, 24-30, 32-40, and 43-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bhat et al (4/1998) in view of Domb et al (US Patent 6,007,845).

Applicants' claimed invention is to a composition, method of making such, and methods of use comprising PLA-PEG biodegradable polymer and a two or three component anchor-adapter-tag system, such as a biotin/avidin or streptavidin system, to which a ligand is attached, such as a peptide, protein, DNA; and a method for the modification

of a biomaterial architecture with and without an adapter segment; and a method for tissue engineering comprising providing a scaffold having a biological ligand attached and contacting cells and seeding cells in a bioreactor.

Bhat et al teach the use of avidin-biotin complexes attached to glass substrates and to which aortic endothelial cells were attached, resulting in increased initial cellular spreading rates and strength of attachment (abstract). Bhat et al does not teach the use of biodegradable polymers with the avidin-biotin complex.

Domb et al teach the use of biodegradable polymers, such as a PLA-PEG nanosphere, to which molecules are covalently bond to the surface for targeted delivery (e.g. Claims 1-13).

In light of Bhat and Domb et al, it would have been obvious to one of skill in the art to make a composition comprising a biodegradable polymer, such as a PLA-PEG complex, and to which a biotin-avidin complex were attached. One would have been motivated to do this to in order to use the composition to facilitate the attachment of the polymer to cells in the hopes of improving the efficacy of tissue differentiation as displayed by Bhat et al. It would also have been obvious to substitute the glass in the Bhat et al invention with a biodegradable polymer, because such were routinely used *in vivo* and in the art of tissue engineering as scaffolds to support cell migration and differentiation.

No claims are currently allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached at (703) 308-0447. The fax number for this Group is (703) 308-0294.

Carrie Stroup

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